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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,448	04/14/2004	Mitchell Weiss	CHOP.0189US	6608

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EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
03/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/824,448	**Applicant(s)** WEISS ET AL.	
	Examiner Joanne Hama, Ph.D.	**Art Unit** 1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 05 March 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *see attached*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-12,39*.
   Claim(s) withdrawn from consideration: *14-38*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

PETER PARAS, JR.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Applicant filed a response to the Final Action of November 30, 2006 on March 5, 2007. The claims have not been entered because claim 9 has been amended and no longer focus on drugs that alter AHSP activity, but on drugs that alter phenotypes of the AHSP mouse. As such, Applicant's response will be applied to the claims filed August 28, 2006. As of the August 28, 2006 claims, claims 14-38 are withdrawn, claim 13 is cancelled.

Claims 1-12, 39 are under consideration.

Maintained Rejections

35 U.S.C. § 101

Applicant's arguments filed March 5, 2007, pages 7-9, have been fully considered but they are not persuasive.

Applicant indicates that claim 1 describes the phenotype of the claimed transgenic animals of the invention. These AHSP knockout animals could be used to identify and screen therapeutic agents which alter the phenotypes associated with AHSP insufficiency. These agents would be useful to restore normal erythrocyte function and could be used to treat human diseases like beta-thalassemia which involved excess hemoglobin production characterized by red blood cell damage and generation of reactive oxygen species which damage cellular proteins. Applicant indicates that the mice of the invention recapitulate key features of the pathology observed in beta-thalassemia, as indicated on page 31, line 12 of the specification, and that the mice of the invention can be used to identify agents which alter AHSP

deficiency in anemia (Applicant's response, page 7, 3rd parag. to page 8, 1st parag.). In response, this is not persuasive. While Applicant indicates that the there is overlap in the pathology of erythrocytes in beta-thalassemia patients and AHSP knockout mice, a screen for drugs to alleviate the symptoms caused by the pathology does not make the claimed mouse's use readily apparent. This is because the etiology of the phenotypes of beta-thalassemia patients and AHSP-deficient mice are different. As such, the compounds identified in the screen, using the claimed mouse, are ones that treat symptoms associated with the AHSP disruption. In addition to this issue, the art teaches that there is no known human condition associated with AHSP that even if compounds are identified using the claimed mouse, an artisan could not use the compounds to treat any human condition associated with AHSP. As such, the claims remain rejected because there is no readily apparent use of the claimed mice.

Applicant indicates that AHSP is identified as a protein that, among other things, protects free alpha-hemoglobin from precipitation which is involved in the formation of alpha-inclusion bodies in Alzheimer's disease (specification, page 14, line 31 through page 15, line 17) (Applicant's response, page 8, 1st parag.). In response, while the specification projects a relationship between AHSP and Alzheimer's disease, nothing in the specification or art teach that there is, in fact, a relationship between the gene and Alzheimer's disease and nothing in the specification indicates that the claimed mice exhibited any Alzheimer's disease.

Applicant indicates that on August 28, 2006, that Applicant indicates that there is an additional utility of the claimed mouse, as describe in Example V, page 69, line 28

through page 73. In this example, AHSP knockout mice can be used to produce AHSP antibodies exhibiting a wider array of epitope specificity. It is noted that Applicant indicates that Examiner Paras agreed that the use of the AHSP knockout mice of the invention to produce anti-AHSP antibodies would also be a credible, specific, and substantial utility (Applicant's response, page 5, 1st parag.). In response, the Examiner does not find using the claimed mice to have specific and substantial utility when used to make antibodies. Rather, using the claimed mice to generate antibodies is a general use of the mice as any knockout mouse can be used to make antibody. This issue was also discussed in the Examiner's Office Action, November 30, 2006, page 3.

Applicant indicates that on page 65, line 19 through page 66, line 15, the inventors disclose that altered AHSP activity is implicated in other human diseases such as hemolytic anemia, and glucose-6-phosphate dehydrogenase deficiency involved in malaria. In response, the Examiner has looked at the cited passages and has determined that the citation indicates possible implications for human disease, but does not teach that AHSP has any role in these diseases. As such, this argument is not persuasive. It is noted that the Examiner has pointed to Viprakaset et al., Office Action, November 30, 2006, pages 4-5, which teaches that there is no known relationship between AHSP and beta-thalassemia. It is noted that Applicant has not responded to the issues presented by Viprakaset et al. As such, the role of AHSP in any disease or disorder is unclear and thus, the use of the claimed mice to screen for compounds to alleviate symptoms associated with AHSP gene disruption is not readily apparent.

For these reasons, the claims remain rejected.

35 U.S.C. § 112, 1st parag.

Applicant's arguments filed March 5, 2007, pages 9-13, have been fully considered but they are not persuasive.

Applicant indicates that the instant specification discloses the preferred methods to generate the transgenic mice presently claimed. Exemplary methods of transgenic animal production are disclosed in the specification (Example II, page 46 of the specification) (Applicant's response, page 11, 3rd parag.). In response, the Examiner was not questioning whether an artisan was able to physically generate the claimed mice, as the methods of knockout technology are known in the art. Rather the issue at hand was that an artisan cannot reasonably predict a phenotype of a transgenic mouse, nor can an artisan predict that a transgenic mouse is a model of human disease. Publications by Doetschmann et al., Moens et al., Jacks et al., Kuehn et al., and Jaenisch et al. were used to illustrate this problem in the art. Applicant indicates that the AHSP knockout mice have abnormal spiculated morphology, reduced life span, increased production of reactive oxygen species, and precipitated hemoglobin (Applicant's response, page 12, 1st parag.). In view of the successful generation of the transgenic mice of the invention with the desired phenotype, it should be apparent that the invention is both fully enabled by the disclosure and that a skilled artisan would know how to use the mouse based on the specification. In response, while Applicant has arrived at a mouse having certain phenotypes, it is unclear whether there is any relationship between the phenotypes and the gene disruption. Note for example, that

phenotypes can arise from unrelated events such as the genetic background of the animal (e.g. see Gerlai publication, page 10 of Office Action, May 23, 2006). Applicant appears to imply that the claimed mice are ready to use because they can be used in drug screens to identify drugs that alleviate their phenotypes. However, exhibiting particular phenotypes without providing any guidance of any relationship between the phenotypes, the gene, and a human disease or condition does not make the mouse ready for use in a drug screen.

With regard to the Examiner indicating that "Applicant indicated that the test compounds or agents are screened for their ability to substitute for AHSP and restore AHSP activity," but indicates that the claims do not read as such, Applicant indicates that claim 9 has been amended such that the screen is used to identify compounds that alter AHSP deficiency-related phenotypes (Applicant's response, page 12, 2nd parag.). In response, the claims have not been entered, and thus, the rejection as it applies to this issue remains.

Thus, the claims remain rejected.

It is noted that Applicant has provided a publication, Kong et al., 2004, The Journal of Clinical Investigation, 114: 1457-1466. However, Applicant has not indicated anything about the publication.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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JH